

Clinically important drug–drug interactions in poly-treated elderly outpatients: a campaign to improve appropriateness in general practice

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Several lists of drug–drug interactions (DDIs) have been used to evaluate *a posteriori* the appropriateness of drug prescription in primary care. However, only rarely are educational campaigns carried out to assess appropriateness prospectively.

WHAT THIS STUDY ADDS

- A multidisciplinary group compiled a list of 53 clinically important DDIs, which (will) serve as a tool to promote (a) awareness and continuous self-assessment by general practitioners and (b) patients management in routine clinical practice.
- This 3 year project promoted by the Local Health Authorities contributed to limit the burden of DDIs in poly-treated elderly patients, especially by reducing potential DDIs that can be avoided and/or minimized in primary care such as those caused by non-steroidal anti-inflammatory drugs.

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AIMS

The aim was to assess the impact of a campaign for general practitioners (GPs) to reduce clinically-important drug–drug interactions (DDIs) in poly-treated elderly patients.

METHODS

We compiled a list of 53 DDIs and analyzed reimbursed prescriptions dispensed to poly-treated (\geq four drugs) elderly (>65 years) patients in the Emilia Romagna region during January 2011–June 2011 (first pre-intervention period), January 2012–June 2012 (second pre-intervention period) and January 2013–June 2013 (post-intervention period). Educational initiatives to GPs were completed in July 2012–December 2012. Pre-test/post-test analysis (2013 vs. 2012) was performed, also using predicted 2013 data ($P < 0.01$ for statistical significance).

RESULTS

Despite the slight increase in poly-therapy rate (16% in 2013, +1.5% from 2011), we found a stable or slightly declining number of potential DDIs for each elderly poly-treated patient (~ 1.5). In 2013, 11 DDIs exceeded 5% of prevalence rate: antidiabetics- β -adrenoceptor blockers ranked first (20.3%), followed by ACE Inhibitors (ACEIs)/sartans-non steroidal anti-inflammatory drugs (NSAIDs) (16.4%), diuretics-NSAIDs (13.6%), selective serotonin re-uptake inhibitors (SSRIs)-NSAIDs/acetyl salicylic acid (ASA) (12.7%) and corticosteroids-NSAIDs/ASA (9.7%). A remarkable reduction emerged for NSAID-related DDIs (diuretics-NSAIDs peaked -14.5% ; $P < 0.01$), whereas prevalence of antidiabetics- β -adrenoceptor blockers increased ($+7.9\%$; $P < 0.01$). When using predicted values, the statistical

significance disappeared for antidiabetics- β -adrenoceptor blockers (+1.3%; $P = 0.04$), whereas it persisted for almost all NSAIDs-related DDIs: ACEIs/sartans-NSAIDs (−3.0%), diuretics-NSAIDs (−6.0%), SSRIs-NSAIDs/ASA (−5.9%).

CONCLUSIONS

This campaign contained the burden of DDIs in poly-treated elderly patients by 1) reducing most prevalent DDIs, especially NSAIDs-related DDIs and 2) balancing the observed rise in poly-therapy rate with stable rate in overall prescriptions of potentially interacting drugs per patient.

Introduction

Drug interactions occur when the effects of one drug are modified by the concomitant or subsequent administration of another agent, by means of drugs (drug–drug interactions, DDIs), food, herbals or any other substance [1]. In clinical practice, there is an important gap between what is theoretically known about DDIs and appropriate management of patients, especially in the elderly who do usually require polypharmacy for co-morbidities.

On one hand, the number of prescribed drugs is a recognized independent risk factor for serious adverse drug reactions (ADRs) in the elderly [2, 3], a vulnerable population with age-related changes in pharmacokinetic and pharmacodynamic parameters, concomitant comorbidities and organ impairments, which increase the risk of hospitalization and mortality [4].

On the other hand, only a fraction of DDIs (that are preventable according to the drug mechanism of action) are clinically important (i.e. they require therapy adaptation and/or they can result in ADRs), and only a minority can be actually avoided by safely removing the potential precipitant agent. In addition, the clinician's perception of the clinical relevance of DDIs is not fully appreciated, thus underestimating relevant risk when multiple drugs are co-administered [5–7]. Finally, the involvement of several prescribers (specialists) in patient care and the availability of disease-specific guidelines increase the likelihood of multi-medications [8] and often preclude general practitioners (GPs) to consider possible drug discontinuation [9].

In this context, polypharmacy is an evolving concept and does not necessarily mean inappropriateness [10], all the more so as intentional co-prescriptions are warranted in certain circumstances to achieve a synergic therapeutic response or counteract ADRs. Therefore, actual de-prescribing is a challenging task in clinical practice.

In the recent past, administrative databases have been largely used to estimate the prevalence of DDIs as

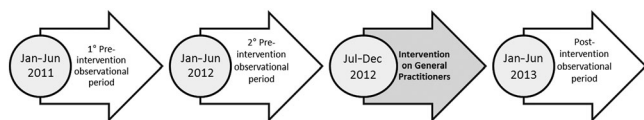
well as to determine possible predictors/determinants of DDI occurrence, especially in elderly under poly-therapy [11, 12]. However, only a limited number of studies have attempted to assess the impact of educational campaigns to improve appropriateness of clinicians' prescriptions, with a non-significant effect of educational outreach programmes on the prescribing rate of potential DDIs [13, 14].

The aims of this study were therefore to 1) compile a list of clinically important DDIs, which may be theoretically modifiable or avoidable, 2) estimate the prevalence of these DDIs in the Emilia Romagna Region (Northern Italy) during the 2011–2013 period and 3) assess the impact of an intervention (active educational campaign) for Italian GPs to manage potential DDIs.

Methods

Study design

This observational study was part of pharmacovigilance projects funded by the Emilia Romagna Region for post-marketing activities aiming at increasing knowledge of ADRs and improving appropriateness. The project was designed/scheduled as follows (Figure 1): 1) creation of the list of potentially interacting drugs (see below), 2) collection and analysis of dispensed data (January 2011–June 2011, first pre-intervention period) to assess prevalence of potential DDI. These data have been shared with GPs as part of the active initiative (see below), 3) collection and analysis of dispensed data (January 2012–June 2012, second pre-intervention period) to evaluate the time trend prevalence, which may be influenced by additional educational campaigns on different topics, 4) implementation of direct educational initiatives to inform GPs and 5) collection and analysis of dispensed data (January 2013–June 2013, post-intervention period) to evaluate whether or not the intervention impacted on prescribers' attitude. To this aim, a one-group pre-test/post-test quasi

**Figure 1**

Project scheduling

experimental study was performed (see the section below on 'data analysis').

Creation of the list of potentially interacting drugs

Currently, a unified validated database of clinically important DDIs does not exist and, in the literature, a number of lists have been published [12, 15, 16].

In this project, a multidisciplinary panel of experts (comprising pharmacists, clinical pharmacologists and pharmacovigilance experts of seven Local Health Authorities-LHAs) compiled a list of potential DDIs. The list was developed to be as comprehensive as possible (so that DDIs susceptible to amelioration can be highlighted) but also manageable for clinicians. The components in the DDI may be a drug class or a single molecule. The following criteria were considered to retain final pairs of DDIs:

(a) clinically important DDIs. The clinical relevance was the leading criterium for selection and took into account potential clinical consequences, the type and quality of supportive clinical data (i.e. DDI potentially causing life-threatening clinical events, with evidence from observational studies). The pharmacological documentation was not considered as a key aspect, although the pharmacological basis of the interaction was annotated;

(b) modifiable DDIs (i.e. existence of therapeutic alternatives); suggestions on measures to control or manage the risk of interaction were also provided. DDIs requiring only clinical monitoring or dose adjustment (i.e. absence of real therapeutic alternatives) were excluded;

(c) measurable through administrative databases; dispensed data refer only to drugs reimbursed by the Italian National Health Service that are prescribed by GPs and dispensed by community pharmacies. Therefore, over-the-counter medications and non-reimbursed drugs were not included (e.g. benzodiazepines);

(d) including at least one agent usually administered for chronic therapies (see below). Each included DDI was characterized by a chronic therapeutic medication (object drug) and a newly-prescribed agent (precipitant drug), which may be administered as acute (e.g. non-steroidal anti-inflammatory drugs - NSAIDs) or chronic treatment (e.g. β -adrenoceptor blockers).

A number of sources were used to assemble the final list. The already existent compendia represented a starting reference. The initial list was subsequently refined through consultation of medical literature (i.e. PubMed), Micromedex and Summary of Product Characteristics.

Data sources

The following administrative databases of seven LHAs of the Emilia Romagna region (Bologna, Ferrara, Forlì, Modena, Parma, Piacenza, Reggio-Emilia), covering about 3 183 000 of inhabitants (22% aged ≥ 65 years), were searched: the Health-Assisted Subjects' Database, containing patients' demographic data and the Outpatient Prescription Database, including all claims for drugs dispensed and reimbursed by the Italian National Health Service. For each subject, information on age, gender, dispensed drugs, prescription date, number of packages and number of units per package was collected. As recommended by the WHO, all drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [17].

Cohort selection and exposure definition

Elderly (aged >65 years) poly-treated patients under chronic treatment were identified as follows:

- Poly-therapy was defined as the exposure to at least five therapeutic classes (using level IV of the ATC classification);
- Chronic treatment was defined as a consecutive drug coverage of at least 90 defined daily doses (DDDs) over the 180 day period. The DDD is a universally adopted technical unit of measurement, which reflects the average adult dose used for the main indication as reflected by the ATC code. DDD number represents a proxy of days supplied [17].

We investigated 'concomitant medication' by defining exposed subjects as those with overlapped prescriptions of two interacting drugs, or drug classes, during the different observation periods [18]. Each patient might be exposed simultaneously or at different times to different DDIs.

Educational initiatives

The intervention was a prescriber-oriented educational campaign, which is also known as academic detailing [19]. From July to December 2012, all GPs in the relevant LHA area were involved in the educational initiatives performed by pharmacists of seven LHAs. The number of interventions ranged from four (Forlì) to 41 (Bologna). Small group meetings [ranging from 15 GPs (Bologna) to 50 GPs (Ferrara)] were planned as part of the routine LHA activity. The purpose of the project and the list of DDIs were presented by a clinical pharmacist, who was assisted by a senior GP in three out seven LHAs. Moreover, by using data of the pre-intervention analysis (January–June 2011), most prevalent DDIs were discussed focusing on measures suggested to control or manage them. Notably, each GP enrolled in the project received the DDI list and individual report, which provided the tabular listing of his/her patients exposed to DDIs during pre-intervention periods.

Data analysis

For different periods of observation (two pre-intervention and one post-intervention periods), we performed data extraction and we computed the prevalence (%) of each DDI included in the list among elderly poly-treated cohorts. In order to estimate the effect of intervention, the one-group pre-test/post-test methodology was used [20]. This quasi experimental methodology consists in the use of a single group of participants (in our study represented by GPs of the seven LHAs) to whom the intervention was given. The measure of the variable (in our study, DDI prevalence in the elderly poly-treated cohort) was performed twice, before and after the intervention (i.e. 2012 and 2013), and relative differences were computed [i.e. (prevalence 2013 – prevalence 2012)/prevalence 2012]. The intervention was considered effective when the pre-test/post-test difference was statistically significant ($P < 0.01$).

To take into account trend variations occurring independently from the intervention, relative differences between two pre-test periods (i.e. 2011 and 2012) were also considered. These differences were used to estimate predicted values of 2013 data in the absence of intervention. Therefore, the relative differences between observed and predicted values (2013 prevalence of each DDI) represented the impact potentially attributable to the intervention.

Results

List of potential DDIs

A total of 53 potential DDIs were retained (Table 1 shows most prevalent DDIs, whereas the full list is provided in Table S1). Vitamin K antagonists and antihypertensive drugs (e.g., diuretics and ACE inhibitors - ACEIs) were most frequently represented as chronic therapy (in nine and seven potential DDIs, respectively), followed by antidepressants (especially selective serotonin re-uptake inhibitors), statins and antidiabetics (five, five and four, respectively). Anti-infectives (especially macrolides, fluoroquinolones and cotrimoxazole) were identified in 17 DDIs as precipitant drugs (i.e. acute administration). In the majority of DDIs, instead of indicating specific therapeutic alternatives, it was proposed to reconsider the need for therapy initiation as proper clinical management (e.g. for DDIs including antidepressants or antibiotics). Pharmacokinetic mechanisms (e.g. cytochrome P450 inhibition) were mostly highlighted as the underlying pharmacological basis.

Prevalence of DDIs

Cohorts of 115 524, 120 023 and 130 083 elderly poly-treated subjects were selected, representing 15.2, 15.6 and 16.7% of the relevant population aged ≥ 65 years in 2011, 2012 and 2013, respectively (Figure 2). No substantial difference was found among the different LHAs. During the three periods, the cohorts were homogenous

in terms of gender distribution (F/M = 50/50), with a mean age of 77.8 years, 37.1, 28.5 and 21.6% of patients aged >80 , 76–80 and 71–75 years, respectively, in terms of mean value during the three periods). In contrast with the increase in the proportion of poly-treatment among the elderly, the average number of DDIs for each patient relatively decreased over time, 1.55, 1.54 and 1.52 in 2011, 2012 and 2013, respectively (Figure 2).

Based on 2013 data, 11 out of 53 possible DDIs exceeded a prevalence rate of 5% (Table 2), 12 ranged 4–1% and the remaining 30 less than 1% (full list in Table S2). The top five ranking DDIs in 2013 were antidiabetics- β -adrenoceptor blockers (20.3%), ACEIs/sartans-NSAIDs (16.4%), diuretics-NSAIDs (13.6%), SSRIs-NSAIDs/ASA (12.7%) and corticosteroids-NSAIDs/ASA (9.7%).

Impact of the intervention

During the 6 month period (July–December 2012), 2375 GPs were involved in the educational initiatives with more than 100 meetings organized by the seven LHAs. By comparing prevalence rates before (2012) and after (2013) interventions, the following most prevalent DDIs resulted in a statistically significant decrease: diuretics-NSAIDs (–14.4%), ACEIs/sartans-NSAIDs (–10.6%), ACEIs/sartans + diuretics-NSAIDs (–13.0%) and SSRIs-NSAIDs/ASA (–5.9%). Conversely, other DDIs showed a significant increase after the intervention, especially antidiabetics- β -adrenoceptor blockers (+7.9%) and clopidogrel-PPIs (+32.3%) (Table 2).

The comparison of two pretest periods (i.e. 2011 and 2012) showed that some trend variations occurred independently from the intervention. However, when the analysis was performed by comparing observed and predicted 2013 data, a statistically significant reduction was maintained for almost all NSAIDs-related DDIs (diuretics-NSAIDs, ACEIs/sartans-NSAIDs, ACEIs/sartans + diuretics-NSAIDs and SSRIs-NSAIDs/ASA). Conversely, the statistical significance disappeared for antidiabetics- β -adrenoceptor blockers (+1.3%; $P = 0.04$) and persisted only for clopidogrel-PPIs. The effects of intervention on the full list of DDIs are presented in supplementary Table S2.

Discussion

To the best of our knowledge, this is the first Italian population-based study showing that prescriptions implying clinically important DDIs in poly-treated elderly patients decreased significantly as a consequence of an *ad hoc* educational initiative for GPs. This finding is mainly driven by the remarkable decrease in prescriptions of NSAID-related DDIs, which persisted even when using predicted data. An additional key result supporting the usefulness of this educational campaign is that, despite the increased prevalence rate of elderly patients exposed to poly-pharmacy (approximately 16% in 2013,

Table 1List of most prevalent DDIs (at least 5% in the 1st semester of 2013) with relevant pharmacological and clinical issues

Chronic-Precipitant drug	Possible clinical consequence(s)	Main mechanism	Management
Antidiabetics-β-adrenoceptor blockers	Unrecognized hypoglycaemic crisis and impaired glycaemic control	Pharmacodynamics	Consider other antihypertensive drug class (e.g. ACE inhibitors) Monitor blood glucose, especially in case of dose modifications
ACEIs/Sartans-NSAIDs	Counteraction of the anti-hypertensive effect, from mild to severe hypertension (depending on underlying patient's clinical status)	Pharmacodynamics	Limit NSAID use, if possible If NSAIDs are required, prefer ASA If only pain relief action is required, prefer paracetamol
Diuretics-NSAIDs	Counteraction of the anti-hypertensive effect (usually mild), hyperkalaemia and possible nephrotoxicity	Pharmacodynamics	Limit NSAID use, if possible If NSAIDs is required, prefer ASA
SSRIs-NSAIDs/ASA	Increased risk of bleeding	Pharmacodynamics	Limit NSAID use Limit the use of SSRIs to major indications
NSAIDs/ASA-corticosteroids	Increased risk of bleeding, fluid retention and hypertension	Pharmacodynamics	Limit NSAID or corticosteroids use
Vitamin K antagonists-PPIs	Increased risk of bleeding	CYP2C9 inhibition	Reconsider PPI use (especially in case of long term administration) Monitor INR and dose modification if needed
ACEIs/Sartans-K⁺ sparing diuretics	Hyperkalaemia	Pharmacodynamics	Reconsider diuretic therapy Prefer thiazides, if feasible Monitor K ⁺ plasma levels
Vitamin K antagonists-Statins	Increased risk of bleeding, myopathy/rhabdomyolysis	Pharmacodynamics and kinetics	Monitor CPK and INR Reconsider the use of statins Decrease statin dose
ACEIs/Sartans + Diuretics-NSAIDs	Renal failure (known as triple whammy)	Pharmacodynamics	Avoid NSAIDs, if possible, especially in patients with pre-existing renal injury and dehydration If only pain relief action is required, prefer paracetamol Monitor renal function (creatinine and K ⁺ plasma levels)
Antidiabetics-Fluoroquinolones	Increased risk of dysglycaemia (both hypo- and hyperglycaemia have been reported)	Pharmacodynamics	Reconsider fluoroquinolone use If fluoroquinolone is the only therapeutic option, consider moxifloxacin (not influenced by renal function)
Clopidogrel-PPIs	Increased risk of thrombosis due to non-activation of clopidogrel (efficacy compromised)	CYP2C19 inhibition	Reconsider PPI use and, in general, gastroprotection, especially if dual antiplatelet therapy is not administered

ACEIs: angiotensin converting enzyme inhibitors; ASA: acetyl salicylic acid; CPK: creatine phosphokinase; CYP: cytochrome P450; INR: international normalized ratio; NSAIDs: non-steroidal anti-inflammatory drugs; PPIs: proton pump inhibitors; SSRIs: selective serotonin re-uptake inhibitors.

+1.5% from 2011), the average number of prescriptions with possible DDIs per patient, based on our list, remained relatively stable (approximately 1.5). These figures diverge from the trend observed by published European studies [9] and latest national prescription data. The Italian Regulatory Agency and the Health and Social Care Information Centre described a considerable increase in prescription rates over the past decade [21, 22], a pharmaceutical phenomenon partially ascribable to disease-specific guidelines [8].

We are aware that statistical phenomena (e.g. regression to the mean) and other factors not related to educational intervention (e.g. variations in disease frequency, marketing pressure by pharmaceutical companies, safety issues and other regulatory measures that may impact the reimbursement status of a given product(s), timing of observations) cannot be ruled out with certainty and

can partially explain a fraction of the variation in our prescription rates [23]. These issues, together with the quasi experimental design of our study, do not allow formal assessment of the impact of the initiative. However, taken together, our findings are consistent with the notion that on-field interventions on GPs are effective in controlling the burden of DDIs, especially those that are caused by unnecessary drugs.

The most remarkable example is provided by NSAIDs, which are known to be frequently administered in chronic pain conditions, for which alternative drugs and/or approaches are available [24]. The clinical relevance of NSAID-associated DDIs is undisputed. A number of studies, including a recent systematic review [25], found that NSAIDs were one of the most frequent drugs involved in DDI-related ADRs, including hospitalization, medication errors and renal injury [26–31].

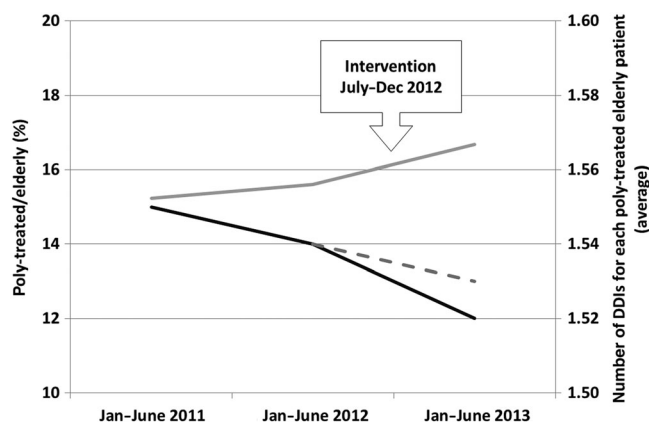


Figure 2

Trend of poly-treated patients on elderly population (grey line) and average number of observed (black line) and predicted (dashed line) DDIs for each poly-treated elderly subject at three time points. — poly-treated/elderly (%), — Number of observed DDIs for each poly-treated elderly patient (average), - - -, Number of predicted DDIs for each poly-treated elderly patient (average)

Although a decrease in the prevalence of NSAID-related DDIs already emerged in the pre-intervention period, the educational intervention generated a sustained statistically significant reduction of almost all NSAID-related DDIs, in particular those including antihypertensive and antidepressant drugs. Therefore, our results underline the importance of therapy reconciliation by clinicians [32, 33], as recently emphasized by the NICE guideline on medicines optimization [34]. Although, based on a recent Canadian survey [35], NSAIDs are not perceived to be a prescribing issue in general practice, we believe that this class should be prioritized for de-prescribing in primary care, all the more so withdrawal reactions and disease rebound are unlikely to occur.

Demonstrating the effectiveness of interventions to improve the appropriate use of polypharmacy in older patients is hardly achievable in clinical practice, especially when performing educational meetings/workshops, which can have small or even unproven benefit [13, 14]. In fact, the latest Cochrane review concluded that '*It is unclear whether interventions to improve appropriate polypharmacy, such as pharmaceutical care, resulted in clinically significant improvement*' [36]. Our initiative is therefore noteworthy, especially if we consider that not all DDIs are avoidable. Depending on the underlying clinical conditions, a number of drugs are intentionally co-prescribed by GPs because the expected benefit is perceived to outweigh the theoretical risk of DDIs. These potentially interacting co-prescriptions are justifiable by adequate risk minimization activities such as clinical and laboratory monitoring.

The beneficial impact of the regional project can be ascribable to (a) the active involvement of clinicians in the project (in particular, the individual feedback with data sharing for self-evaluation as part of the educational campaign), (b) offering practical alternatives in terms of

Table 2

Most prevalent DDIs (at least 5% in the 1st semester of 2013): prevalence rate and intervention effects

Drug-drug interaction	Observed prevalence *			Pre-test-post-test comparison Δ (13-12)/12 (P value)	Trend variations independently from intervention Δ (12-11)/11 (P value)		Predicted prevalence†	Effect potentially attributable to the intervention‡ Δ (13 _{obs} -13 _{pre})/13 _{pre} (P value)	
	2011	2012	2013				2013		
Antidiabetics- β -adrenoceptor blockers	17.5%	18.8%	20.3%	+7.9% (<0.01)	+7.1% (<0.01)		20.0%	+1.3% (0.04)	
ACEIs/sartans-NSAIDs	19.7%	18.3%	16.4%	-10.6% (<0.01)	-7.2% (<0.01)		16.9%	-3.0% (<0.01)	
Diuretics-NSAIDs	17.2%	15.8%	13.5%	-14.4% (<0.01)	-8.2% (<0.01)		14.4%	-6.0% (<0.01)	
SSRIs- NSAIDs/ASA	13.5%	13.5%	12.7%	-5.9% (<0.01)	+0.0% (0.97)		13.5%	-5.9% (<0.01)	
NSAIDs/ASA-corticosteroids	9.3%	9.4%	9.7%	+2.7% (<0.01)	+1.9% (0.16)		9.6%	+0.8% (0.35)	
Vitamin K antagonists-PPIs	8.2%	8.5%	8.9%	+3.9% (<0.01)	+4.0% (<0.01)		8.9%	-	
ACEIs/sartans-K ⁺ sparing diuretics	8.6%	8.3%	8.2%	-0.8% (0.55)	-3.1% (<0.01)		8.0%	+2.4% (0.01)	
Vitamin K antagonists-statins	6.9%	7.3%	7.7%	+4.4% (<0.01)	+6.3% (<0.01)		7.8%	-1.4% (0.16)	
ACEIs/sartans + diuretics-NSAIDs	8.5%	7.8%	6.8%	-13.0% (<0.01)	-7.9% (<0.01)		7.1%	-4.9% (<0.01)	
Antidiabetics-fluoroquinolones	5.5%	5.6%	5.8%	+3.1% (0.07)	+2.8% (0.11)		5.8%	-	
Clopidogrel-PPIs	3.2%	4.2%	5.6%	+32.3% (<0.01)	+32.1% (<0.01)		5.2%	+6.4% (<0.01)	

* estimated on the poly-treated elderly patients; † predicted by using trend variations independently from interventions; ‡ computed comparing observed (obs) and predicted (pre) values; ACEIs: angiotensin converting enzyme inhibitors; ASA: acetyl salicylic acid; NSAIDs: non-steroidal anti-inflammatory drugs; PPIs: proton pump inhibitors; SSRIs: selective serotonin re-uptake inhibitors.

overall management of patient's therapy (we have adopted a compromise between indicating certain medication choices, when strong evidence exists, to simple suggestion of proper risk – benefit evaluation of the drug) and (c) no additional campaigns on appropriateness were carried out during the 3 year period at the local level (multiple initiatives may decrease the chances of a successful intervention).

It is worth noting that only local educational activities were previously performed on the interaction between clopidogrel and PPIs, which was highly debated during the period of the analysis and is still controversial [37]. This may also explain the observed steadily increasing prescription rate, which may indicate a change in the degree of clinicians' confidence in its actual clinical importance. By contrast, the observed increase in prescription rate of antidiabetics/ β -adrenoceptor-blockers is likely to reflect a two-fold phenomenon: 1) the systematic application of disease-specific guidelines to patients with comorbidities, which calls for innovative interactive approaches to the production and dissemination of guidelines [38] and 2) uncertainty of GPs in the actual clinical relevance of this drug–drug combination. In fact, although this DDI is well recognized in the summary of product characteristics and in the literature (i.e. unrecognition of hypoglycaemic crisis and impaired glycaemic control [39]), β -adrenoceptor blockers are used and recommended in diabetic patients when concomitant stable heart failure exists or recent acute myocardial infarction occurred. Therefore, only rarely can this theoretically avoidable drug–drug combination be modified. Clinical judgment is required on a case-by-case basis. This case also exemplifies the real clinical scenario, where two drugs may be intentionally co-prescribed because the recognized (but theoretical) risk of DDIs can be controlled by adequate clinical monitoring.

In the recent past, similar population-based studies raised concern on the correlation between poly-pharmacy and inappropriateness in elderly [40–42]. The prevalence rate found in our cohort falls at the low end of the range reported in previous studies in out-patients. Although a direct comparison among the different poly-pharmacy rates is cumbersome and hard to interpret (studies may differ in terms of definition of poly-therapy, sample age, nature of data source, units of analysis, variations in clinical practices and patients' behaviours among the different Countries), our data remarkably differ from a similar investigation performed on 2007 prescription data of the Emilia Romagna region (39%) [43] and are more in line with most recent European and US studies, showing that 16% of the study population were exposed to drug combinations [44–48].

Discussing the reliability of our list and its validity in other settings is beyond the aim of this study, all the more so as a comprehensive list strongly depends on

the drugs available on the market, their prescribing pattern in each local context as well as the drug interaction compendia used for this purpose [49], thus making comparisons among different settings most likely irrelevant. Nonetheless, we attempt to adopt a multidisciplinary systematic evidence-based approach, as recently suggested by major experts in the field [50]. This list should not be viewed by clinicians as an administrative audit, but rather can serve as a tool to (a) support individual (self)assessment of GPs, (b) facilitate individual patient management during routine clinical practice and (c) routinely monitor the prevalence of DDIs over time and check the long lasting effect of intervention and/or the need for additional targeted strategies.

Limitations

Clinical, regulatory and public health implications should be carefully balanced against known limitations of the study and especially its quasi experimental design, implying the lack of random selection of prescribers and control group, which does not allow formal quantification of the effect of the intervention. Another inherent limitation of this pharmaco-epidemiological approach relies on data source. In fact, the use of dispensed data may cause a possible overestimation of the actual exposure, since some dispensed doses may escape actual administration to patients. However, this is likely to be a minor issue when analyzing drugs for chronic therapies.

We are also aware that our 3 year project required several time-consuming activities (i.e., three different periods of observation and analyses, involving regional drug service, academia, clinical pharmacists and general practitioners). Nonetheless, we believe that efforts used in this preliminary phase to set-up activities and methodological issues can serve as the basis to facilitate future pharmacovigilance projects with similar purpose.

We have demonstrated the early effect of the educational campaign, which should be re-evaluated to check whether or not a long lasting beneficial effect is maintained.

It should be also recognized that potential DDIs far outnumber actual drug interactions [4]. The final occurrence of the clinical event depends on a number of additional risk factors. Nonetheless, the evaluation of the actual clinical relevance of DDIs is beyond the aim of this study, although the majority of DDIs in our list are widely recognized to be clinically important, as previously discussed [30].

NSAIDs, for which we have the most remarkable results, have been evaluated as a class, with no specific data on a given pharmacological agent, which may have a different safety profile. Nonetheless, the NSAID-related interactions are with regards to cardiovascular and renal complications, for which no clinically significant differences exist among the different compounds (with the exclusion of cardiac risk with selective COX-2 inhibitors

and diclofenac). In addition, we cannot precisely identify relevant therapeutic indications (i.e. whether or not NSAIDs were prescribed for acute or chronic diseases), although we expect that a large proportion of patients were exposed to long term treatment considering that reimbursed data have been used. Another key methodological aspect regards the amount of NSAIDs sold as over-the-counter, which was not captured by our analysis. We cannot speculate whether or not the effect of the intervention is over- or underestimated.

Finally, there are two methodological aspects to be mentioned: (a) reimbursed drugs may have been theoretically prescribed also by hospital clinicians, thus GPs could be unaware of the overall prescription pattern of individual patient. However, to the best of our knowledge, the contribution of hospital physicians is expected to be negligible and (b) non-reimbursed drugs (e.g. benzodiazepines) are not captured by administrative databases. In particular, we believe that the use of benzodiazepines warrants future investigation through appropriate data sources (e.g. analyses of nursing home care), considering their heterogeneous therapeutic uses and regulatory status requiring harmonization across Europe [51].

In summary, this educational initiative carried out in Emilia Romagna reached the goal of reducing inappropriate prescriptions derived from clinically important DDIs in poly-treated elderly patients. This was achieved by 1) reducing primarily NSAIDs-related DDIs, one of the most prevalent DDIs that can be avoided and/or minimized in primary care and 2) maintaining a stable overall prescription rate of potentially interacting drugs per patient, despite the observed rise in poly-therapy rate.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). They declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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EP supervised the project and is guarantor for the study. All authors provided substantial contribution to data interpretation and their discussion. They critically revised the content and approved the final version of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1

Full list of 53 DDIs identified for the study, listed by decreasing order of prevalence in 2013

Table S2

Prevalence rate and intervention effects for all studied DDIs, listed in decreasing order of prevalence (2013 data)